General Pharmacology

- Pharmacokinetics
- Pharmacodynamics
- Drug-drug interactions

1. **Pharmacokinetics:** Describe what the body does to the drug. This includes: absorption, distribution, biotransformation and excretion of durg.
2. **Pharmacodynamics**: Describe what the drug does to the body. This includes the mechanism of action, pharmacological action, adverse effects, and the pharmadodynamic drug-drug interaction.
3. **Pharmacotherapeutics:** Describe uses of drug for prevention, diagnosis and treatment of diseases.

Drug: Chemical substance that affects biologic systems of living organism.

Drug nomenclature:

الاسماء التجارية مش مطلوبة

1. **Chemical name:** Describe chemistry of the drug e.g. acetyl salicylic acid.

2. **Generic (Non-proprietary or approved) name:** This is the abbreviated and approved name of the drug. It is the official medical name assigned by the *producer* in collaboration with the food & Drug Board and Nomeneclature committee. Each drug has *only one name* all over the world and it is not capitalizes e.g. aspirin, atenolol, amlodipine, and captopril. *Very few drug have two generic names e.g ("paracetmol-acetaminophen", "neostigmine-prostigmine", "epinephrine-adrenaline", "norepinephrine-noradrenaline", "meperidine-pethidine").*

3. **Brand (Proprietary or Trade) name:** These are names given to the drug by the manufacturing and marketing company, and they are *copyrighted* terms selected by the manufacturer e.g. Aspocid, Inderal, Tonormin, Myodura, and Capoten.

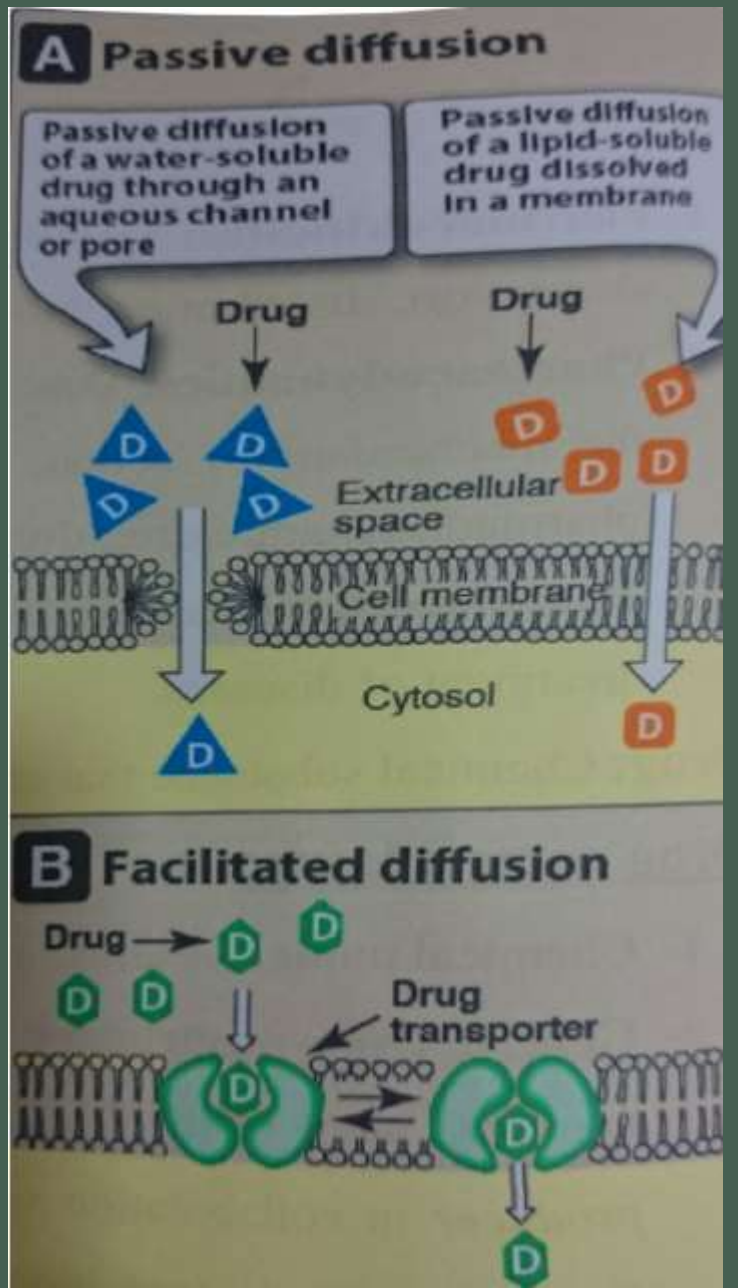
PHARMACOKINETICS

ABSORPTION

Definition: Passage of drugs from site of administration to systemic circulation.

the mechanisms of drug absorption follow the mechanisms of drug movement across the biological membranes, which include:

- **Passive diffusion:** The most common and most important mechanism, it includes:
  - **A.** Rapid movement of lipid-soluble drug across the cell membrane.
  - **B.** Movement of water-soluble drugs across the aqueous channels (water pores).



2. Facilitated diffusion:

- No energy is required as the drugs are carried to inside of the cell ***according to the concentration gradient*** by :

a. Carrier protein.

b. Drug transporter.

3. Active transport:

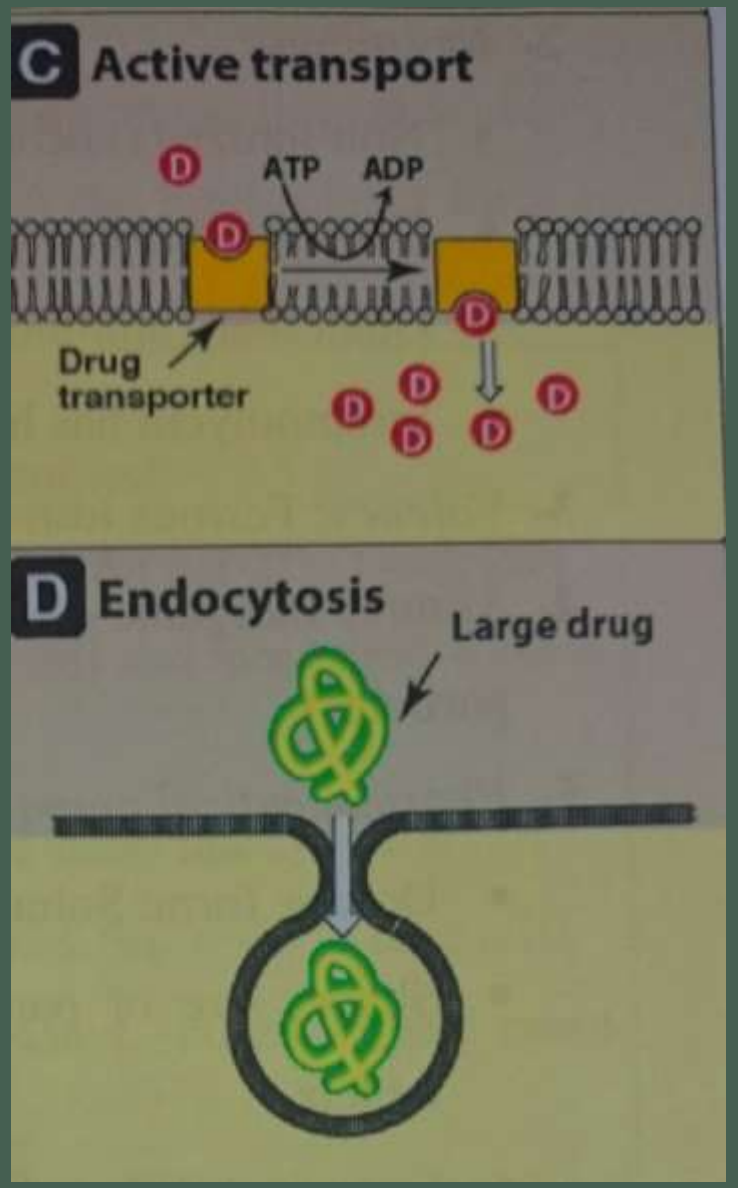
Energy is required because the drug movement may be ***against the concentration gradient*** by :

a. Drug transporter.

b. P-glycoprotein drug transporter extrudes drug outside the cells, and it is responsible for drug resistance.

4. Endocytosis and exocytosis:

Usually occur by drugs of high molecular weight. The drug binds to the cell membrance, dips in and enveloped by the cell membrane, a tear in the cell membrane allow the drug to move inside/ outside the cell.
The tear is healed immediately.



2. Factors affecting absorption:

A) Factors related to the patient:

1. Route *of administration:* I.V. and inhalation > I.M. > S.C. > Oral > Topical.

2. Absorbing surface:

- Vascularity (Alveoli > Skeletal muscle > S.C.tissue).
- Surface area (Alveoli > Intestine > Stomach).
- Pathological conditions: Diarrhea & malabsorption → ↓ oral absorption.

3. Systemic circulation :
H.F. & shock → ↓ absorption → oral and I.M. routes are not suitable.

4. Specific factors: Intrinsic factor is essential for vitamin B12 absorption.

B) Factor related to the drug:

1. Water and lipid solubility:

- Both are needed for absorption
- Completely water-soluble compounds are not absorbed (e.g. barium chloride).
- ↑Lipid solubility → ↑ absorption (lipid /water partition coefficient)

2. Ionization:

- Non-ionized (uncharged) → better absorption
- Depends on *pKa of the drug* and *pH of the medium*
- Quaternary ammonium compounds → ionized → poor absorption
- Streptomycin has high pKa → always ionized → not absorbed orally

3. Valency : Ferrous iron (Fe^{+2}) is absorbed better than ferric iron (Fe^{+3})

4. Nature: Inorganic compounds (small particles) > organic compounds (large particles)

5. Pharmaceutical preparation:

- Dosage form: Solution > Suspension> tablet
- Shape, size of particles and rate of disintegration and dissolution of tablets
- Excepient (filler): Ca^{+2} salts → ↓ oral absorption of tetracyclines

Passive diffusion:

- The most important means by which drugs are absorbed from sites of administration & distributed within the body.
- It depends mainly on: * Lipid solubility * Non-ionization of drugs
- **Ionization of the drug:**
  - The charge of ionized drug attracts water with formation of water-soluble [lipid-insoluble] complex. *The unionized drug is lipid soluble*.
  - A very large percentage of the drugs in use are weak acids or weak bases.
  - Weak acids are unionized when protonated [bind hydrogen] while weak bases are unionized when unprotonated

$HA \longleftrightarrow A + H^+$ **<u>while</u>** **$B + H^+ \longleftrightarrow BH^+$**

For weak acid or weak bases**: log protonated/unprotonated = pKa –pH**

The pK_a is that pH at which the concentrations of the ionized and unionized forms are equal. pK_a is specific for each drug and can be obtained from pharmacokinetic tables.

- The lower the pH relative to the pK_a, the greater will be fraction of drug in the protonated form so, weak acid are unionized while weak bases are ionized.

- So, more weak acid will be unionized and in the lipid-soluble form at acid pH, where as more basic drug will be unionized and in the lipid-soluble form at alkaline pH.

Examples:

- **Aspirin** [acid] has pKa=3.5 and pH in the stomach=2.5

pKa - pH =log protonated/unprotonated. So 3.5-2.5=1=log10/1
So aspirin is more protonated [unionized] and more lipid-soluble in the stomach.

- Pyrimethamine [base] has pKa=7 and pH of small intestine=8

pKa - pH =log protonated/unprotonated. So, 7-8= -1=log1/10
So Pyrimethamine is more unprotonated, unionized and more lipid-soluble in small intestine

Clinical importance of pKa:

1. **GIT:**

- Aspirin (acid drug) is mostly non-ionized in the empty stomach crosses the cell membrane of gastric mucosal cells. In gastric mucosal cells the pH is alkaline, so aspirin becomes ionized (lipid insoluble)and cannot cross the cell membrane → Aspirin is trapped in gastric mucosal cell → death of these cells inducing "peptic ulceration"

2. **Kidney**:

- In drug poisoning, renal drug elimination can be enhanced by changing urinary pH to increase ionization of the drug and decrease lipid solubility and inhibit tubular reabsorption.
- Alkalininzation of urine (to increase urine pH above drug pKa) is useful in acidic drug poisioning e.g. aspirin and phenobarbital.
- Acidification of urine (to decrease urine pH below drug pKa) is used in basic drug poisoning e.g. amphetamine.

In conclusion:

- Absorption of drugs is mostly by simple diffusion through lipid membranes.
- Ionized form of the drug is water-soluble and cannot pass lipid membranes except through water filled pores which is too narrow to allow large molecules to pass.
- Non-ionized form of the drug is lipophilic and can easily cross lipid membranes.

Bioavailability

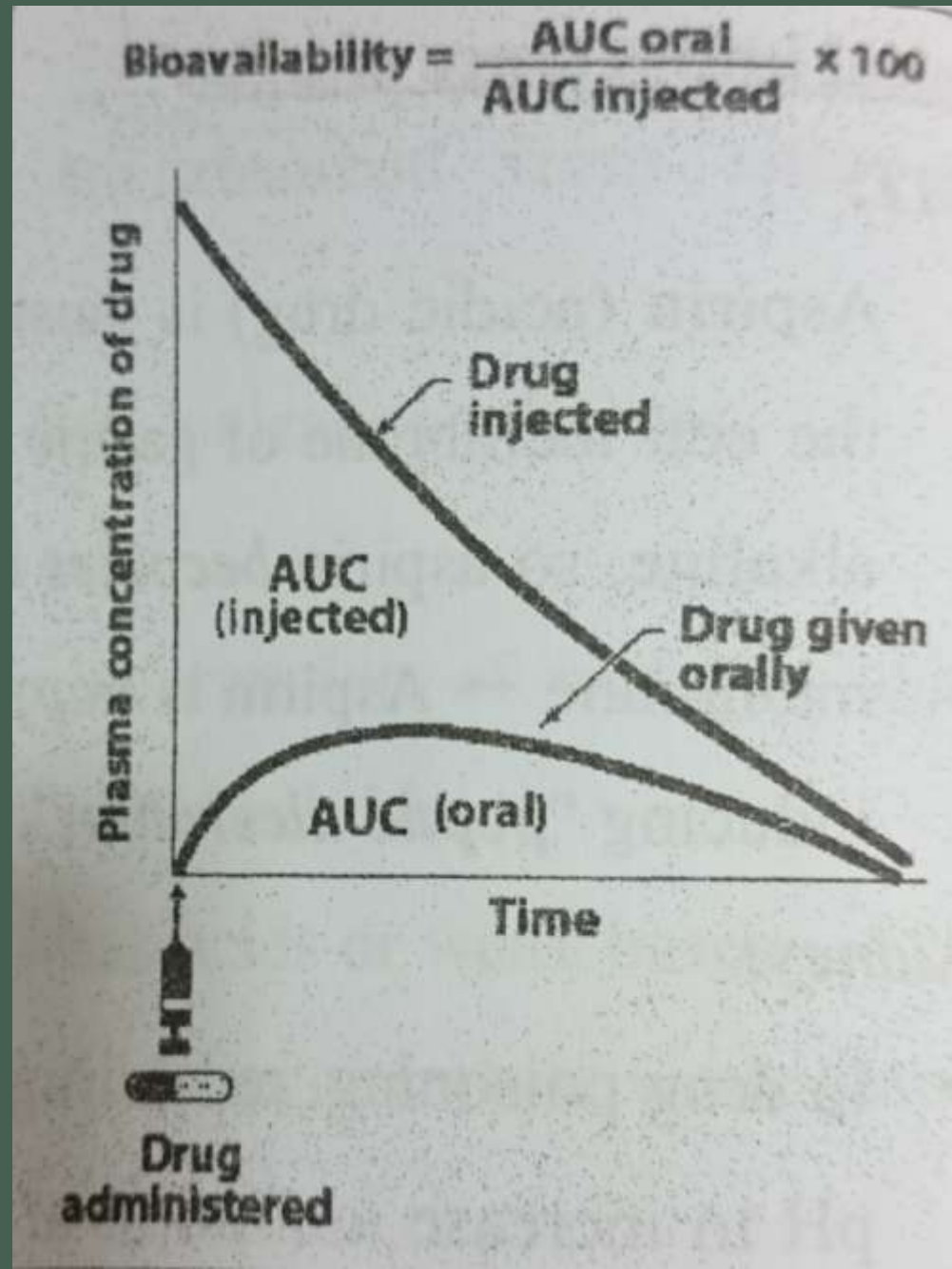
It is the percentage of drug that reaches the systemic circulation and becomes available for biological effect.

$$\text{Bioavailability} = \frac{\textbf{Area under the curve (AUC) after oral route}}{\textbf{Area under the curve (AUC) after L.V. route}} \times 100$$

Factors affecting bioavailability:

1. **The extent of drug absorption.**
2. **1st pass effect(1st pass metabolism):**

- It is the metabolism of some drugs in a single passage through gut wall, liver or lungs before reaching systemic circulation.



A. **Hepatic 1st pass effect:**

- Nitroglycerin and propranolol pass from GIT to liver where they are extensively metabolized in their 1st pass through liver before reaching systemic circulation.

B. **Intestinal 1st pass effect:**

- Estrogens are extensively metabolized in their 1st pass through intestinal wall.

C. **Pulmonary metabolism:**

- After inhalation, nicotine is partially metabolized in the lung.

DRUG DISTRIBUTION

After absorption the drug is distributed through 3 body compartments:

A. **Vascular compartment = small volume of distribution** (4 litres in 70 kg person): drugs distributed in this compartment are ***hydrophilic*** (lipid/water partition coefficient is low), and most of the drug is ionized at the plasma pH e.g. heparin.

B. **Vascular and interstitial compartments =Moderate volume of distribution** (14 Litres in 70 kg person): drugs distributed in these compartments are ***hydrophilic*** (lipid/water partition coefficient is low), with lesser degree of ionization at plasma pH e.g. neostigmine.

C. **Vascular and interstitial and intracellular compartments =Large volume of distribution** (Total body water about 40-42 Litres in 70 kg person): drugs distributed in these compartments are ***non-ionized and lipophilic*** (lipid/water partition coefficient is high) e.g. barbiturates.

Blood –brain barrier (BBB): (brain capillary endothelium with tight inter-cellular pores & adjacent glial tissues).

- Only lipid-soluble & non-ionized drugs can pass blood-brain barrier.
- Inflammation (meningitis) increases permeability of BBB (The concentration of penicillins & cephalosporins in the CSF of normal subjects is 0.5 -1 % of plasma level, this could increase up to 5% in case of meningitis).

Placental barrier: Drugs that pass placental barrier may cause:

- *During pregnancy* ⟶ Teratogenicity, embryotoxicity
- *During labor* ⟶ Neonatal asphyxia ,neonatal jaundice (Kernicterus)

Redistribution:

- Occurs with highly lipid-soluble drugs as thiopental. After initial distribution to CNS, thiopental redistributes to less perfused tissues e.g. skeletal muscle and fat, ending its action.

- *Importance*: repeated administration → Tissue saturation → CNS accumulation → Toxicity.

VOLUME OF DISTRIBUTION (Vd)

- It is a theoretical expression, defined as the apparent volume that would accommodate the entire amount of the drug in the body in a concentration equal to that of plasma.

$$V_d = \frac{\text{Amount of the drug in the body}}{\text{Plasma concentration}}$$

Factors affecting distribution of drugs:

1. Blood flow (perfusion): Amount of drug delivered to particular organ depends on the blood flow to that organ (Blood flow distribution)
2. Lipophilicity (diffusion): The ability of the drug to diffuse across cell membranes depends on its lipophilicity (⬆ lipophilicity ➡ ⬆ distribution)

Characteristic of Lipophilic drug:

1. Well- absorbed orally.
2. Usually subjected to hepatic 1st pass effect.
3. Eliminated mainly by liver (hepatic elimination).
4. Crosses blood-brain, and placental barriers.

3. **Plasma protein binding (PPB):** Drug in blood exists in two forms:

- **PP bound form:** inactive, non-diffusible and cannot be metabolized or excreted.
- **Free form:** active, diffusible and can be metabolized or excreted.
- The two forms exist in equilibrium, when fraction of the free form is metabolized or excreted similar fraction is released from plasma protein binding sites.

Characteristics of drug with high PP binding:

- PP bound fraction cannot be eliminated and acts as reservoir.
- Because the plasma protein binding sites are limited, drugs which bind to albumin can displace each other leading to clinically significant interactions.

- Aspirin and other drugs (e.g. amiodarone) displace warfarin from its PP binding sites. Since warfarin has a small free fraction (1%) and highly PP bound fraction(99%),the displaced portion may be dangerous (if 99% is displaced, the active part of the drug increased 100%)

1. Binding to tissue constituents (Tissues affinity): It is due to affinity of drugs to some cellular constituents.

- Chloroquine is concentrated in liver.
- Iodides are concentrated in thyroid and salivary glands.

Importance of V_d:

- Calculation of the ***loading dose of a drug = (desired plasma Css) X (V_d).***
- Calculation of the **corrective dose of a drug =**
  (desired plasma Css –achieved plasma level) X (V_d).

- **In both circumstances, if the drug is not given by IV route the value should be divided by the bioavailability of the drug by the given route.**

3. In treatment of drug toxicity:

- **Dialysis is not useful for drugs with high V_d (most of the drug is in the tissues).**
- **Hemodialysis is useful for drugs with low V_d (most of the drug is in the blood).**
- **Peritoneal dialysis is useful for drugs with moderate V_d**
- **V_d of a drug is directly proportionate to half life of the drug: $t_{1/2}$= 0.693 V_d/Cis**

(Cls= *Drug Clearance*, **Css=** *drug steady state plasma concentration*)

BIOTRANSFORMATION (METABOLISM)

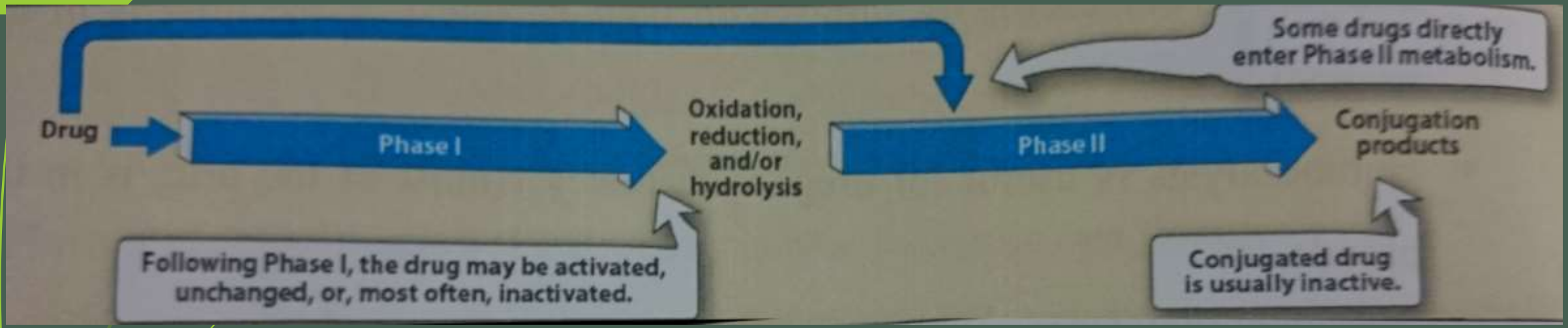
- These are changes that occur to drugs after absorption until excretion.
- Drug metabolism occurs mainly in the *liver*.
- The aim of drug metabolism is the conversion of ionized drugs to non-ionized, water-soluble metabolite which is *easily excreted*

Consequences of drug metabolism:

1. Convert ***active*** drug to ***inactive*** metabolite (most drug).
2. Convert ***inactive prodrug*** into ***active drug*** e.g. enalapril → enalaprilat (active) & prednisone → prednisolone (active).
3. Convert in***active*** drug to ***active*** metabolite e.g. codeine → morphine.
4. Convert drug to **toxic** metabolites e.g. halothane & paracetamol → toxic epoxides which are conjugated with glutathione. Glutathione deficiency may precipitate paracetamol or halothane hepatotoxicity.

الامثله هون ركزت عليهم وحكت رح تجيبهم

Types of biotransformation reactions:



Phase I (functionalization) reactions:

- Phase I reaction include: oxidation, reduction and hydrolysis.
- **The** most important reaction is oxidation by cytochrome p_{450} (CYP) oxidases.
- **Phase** I reaction result in conversion of active drug to inactive metabolite (some times convert the prodrug to active drug). If the metabolite is water-soluble it is excereted, if not, it enters phase II.

- **Phase II (biosynthetic "conjugation") reactions:**
- An endogenous substrate (e.g. glucronic acid, sulfate, glutathione, amino acids, or acetate.) is conjugated with the parent drug or its phase I metabolite.
- This result in formation of non-toxic, highly polar (ionized), water-soluble and rapidly eliminated conjugates.

Metabolizing enzymes:

A. Microsomal enzymes e.g.
   - Cytochrome P_{450} oxidases and their family ① & subfamily ② (CYP 2① C9②).
   - Glucuronyl transferases for conjugation.

B. Non-microsomal enzymes e.g. dehydrogenase, esterases (plasma) & xanthine oxidases (cytoplasm).

Factors affecting biotransformation:

1. Physiological changes (age & sex).
2. Pathological factors (liver cell failure).
3. Pharmacogenetic variation in metabolizing enzymes e.g. slow and fast acetylators.
4. Enzyme induction & enzyme inhibition.

Enzyme induction:

- Many drugs are able to include (increase activity) of microsomal enzymes resulting in **increased rate of metabolism of** the inducing drug as well as other drugs metabolized by microsomal enzymes.
- **Some inducing drugs:**

- Phenobarbitone
- Phenytoin
- Carbamazepine
- Rifampicin
- Nicotine

Consequences of enzyme induction:

1. **failure of drug action:** Rifampicin (enzyme inducer) may enhance metabolism of progesterone and warfarin.

2. Increase metabolism of the inducing drugs. This leads to tolerance e.g. phenobarbitone.

3. Increase metabolism of endogenous substrate e.g. phenobarbitone may be used to enhance eliminiation of bilirubin in physiological jaundice.

4. **Drug interactions:**

- Rifampicin enhances metabolism of warfarin, and may lead to failure of contraception (enhance metabolism of progesterone).
- Antiepileptics increase the metabolism of each others and the combination may lose its efficacy gradually.
- Prolonged use of enzyme iducers may produce rickets or osteomalacia due to increased metabolism of vitamin D.

- Enzyme induction is reversible. It occurs over few days and passes off over 2 – 3 weeks after withdrawal of inducer.

Enzyme inhibition:

- Many drugs inhibit activity of microsomal enzymes resulting in decreased rate of metabolism of other drugs i.g. potentiate their pharmacological actions.
- Some enzyme inhibitor drugs:

- Erythromycin	- Climetidine	- Ciprofloxacin
- Contraceptive pills	- Allopurinol	- Na^+ valproate

- **Consequences of enzyme inhibition on metabolized drugs:**

1. Exaggerated pharmacological action.
2. Exaggerated adverse effects.
3. Increased duration of action and half life of some drugs.
4. Drug-drug interactions.

EXCRETION OF DRUGS

Kidney is the most important organ for excretion. Excretion occurs through:

1. Glomerular filtration:
   All free drug molecules whose size is less than the glomerular pores are filtered into bowman's capsule.
2. Proximal convoluted tubules (PCT):

- Secretion of drugs occurs primarily in the PCT by energy-dependent active transport systems.
- Active secretion occurs either through acid carrier e.g. for penicillin, probenicid & salicylic acid or basic carrier for amphetamine &quinine.

3. Distal convoluted tubules:

- Lipophilic drugs may be reabsorbed back to systemic circulation.
- Alkalinization of urine (by $NaHCO_3$) keeps acidic drugs ionized and increases their excretion.
- Acidification of urine (by ascorbic acid "Vit.C" or ammonium chloride) leads to ionization of weak bases and enhancement of their excretion.

Other sites of excretion:

1. **Bile: with enterohepatic recycling** e.g. rifampicin, doxycycline, ciprofloxacin & azithromycin, or without enterohepatic recycling e.g. ceftriaxone and cefoperazone.
   - Biliary excretion of these drugs increased their efficacy in treatment of enteric and biliary diseases.
2. Lungs e.g. volatile anesthetics.
3. Saliva e.g. iodides.
4. Sweat e.g. rifampicin.
5. **Milk:** this is important in lactaaing mothers.

Examples of drugs contraindicated during breast feeding:

1. **Antibiotics:** chloramphenicol, tetracyclines & sulfonamides.
2. **CNS drugs:** Narcotics, benzodiazepines, alcohol & nicotine.
3. **Laxatives:** Cascara & senna.
4. **Corticosteroids:** They suppress baby's growth and immunity.
5. **Bromocreptine:** It suppresses lactation.
6. **Sex hormones:** Contraceptive pills suppress lactation.

Note: To decrease risk to infants, lactating mothers should take drugs immediately after nursing or 3 – 4 hours before next feeding.

Note: pH of milk is more acidic than that of plasma basic drugs accumulate in milk. Also, milk contains more fat which leads to retention of lipid-soluble drugs e.g. cytotoxic drugs, metronidazole, morphine and laxatives.

PARAMETERS OF ELIMINATION

(1) KINETICS ORDERS

1- First order kinetics (for most drugs):

1. Rate of elimination is directly proportionate to the blood concentration of drugs i.e. constant percentage of the drug is eliminated per unit of time.
2. Constant "$t_{1/2}$" (elimination half life)
3. Repeated dosing increases drug concentration and accordingly the rate of elimination increases till the rate of administration equals the rate of elimination. At this point Css (steady state concentration) is reached.
4. After 4 – 5 $T_{1/2}$ more than 95% of Css is reached.
5. Css is directly proportionate to the dose (↑ dose → ↑ Css).
6. Most drugs obey 1st order kinetics.

2- Zero-order kinetics: (Example: *digitalis glycosides)*

1. Rate of drug elimination is constant i.e. constant amount of drug is eliminated per unit of time.
2. "$t_{1/2}$" (half life) is not constant.

3. No Css is reached by repeated dosing.

4. Any change of the dose may cause toxicity.

Note: some drugs follow 1st order kinetics in small dose and zero order kinetic at large doses i.e. the elimination mechanism is said to be saturated (saturation kinetics).

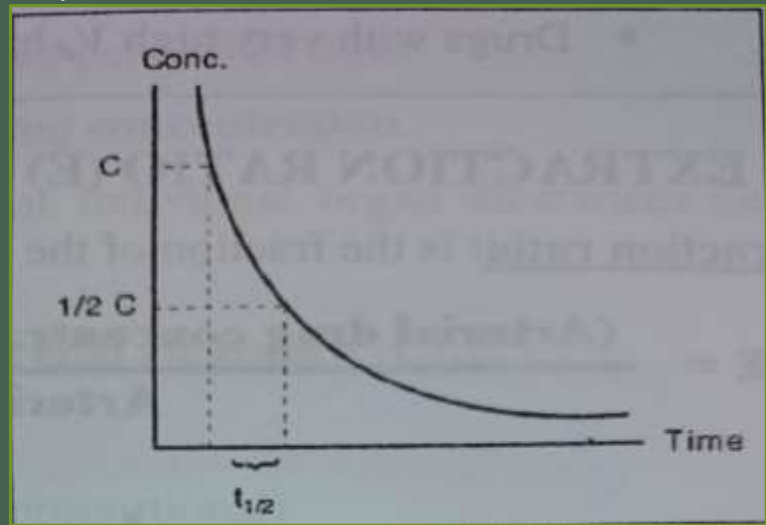
Importance of saturation kinetics:

1. Modest change in dose or bioavailability may cause unexpected toxicity.
2. Drug-drug interactions are common.
3. Drugs obeying saturation kinetic : phenytoin, salicylate and theophylline.
4. These drugs need monitoring of their plasma levels to avoid toxicity.

(2) ELIMINATION HALF LIFE ($t_{1/2}$)

It is the time required to reduce the plasma concentration of the drug to half the initial concentration (the time required for drug concentration to be changed by 50%).

$$t_{1/2} = 0.693 \ V_d / CLs$$



Importance of elimination $t_{1/2}$:

1- It determines the dosage interval (T).

- if T = "$t_{1/2}$"
- if T < "$t_{1/2}$" → drug accumulation may occur.
- if T > "$t_{1/2}$" → drug concentration decreases between doses.

2- It indicates time required to attain Css (about 4-5 $T_{1/2}$) :

- If the drug is aadministered every "$t_{1/2}$" :
  - After the 1st "$t_{1/2}$" , drug concentration reaches 50% of the final Css.
  - After the 2nd "$t_{1/2}$" , drug concentration reaches 75% Css.
  - After the 3rd "$t_{1/2}$" , drug concentration reaches 87.5% Css.
  - After the 4th "$t_{1/2}$" , drug concentration reaches 93.75% & 96.87% Css .
- Therefore, one can assume that if the if the drug is given every "$t_{1/2}$". Css will be reached after 4-5 "$t_{1/2}$"s.

3- If "$t_{1/2}$" is very short (seconds or minutes), the drug should be given by IV infusion (e.g. dobamine, dobutamine, esmolol).

4- If "$t_{1/2}$" is very long , the drug should be administered in loading dose to reach the desired Css rapidly followed by maintenance dose to maintain the desired Css.

Factors affecting elimation "$t_{1/2}$" :

1. State eliminating organs i.e. liver & kidney function.
2. Delivery of drugs to the eliminating organs:
   - Plasma protein binding limits drug elimination.
   - Drugs with very high V_d have limited elimination.

(3) EXTRACTION RATIO (E) & HEPATIC CLEARANCE (CL_{liver})

Extraction ratio: is the fraction of the drug eliminated by the liver.

$$E = \frac{(Arterial\ drug\ concentration) - (Venons\ drug\ concentration)}{Arterial\ drug\ concentration}$$

$$Extraction\ ratio = \frac{amount\ extracted}{amount\ entered} = \frac{Q\ X\ (CA - CV)}{Q\ X\ CA}$$

Amount entered = Q X C_A Amount exit = Q X C_V

Amount extracted = Q (C_A – C_V)

Q: blood flow – C_A : Atreial concentration – C_V: Venous concentration.

- When E > 0.6 ➔ Clearance is nearly flow-dependent e.g. propranolol.
- When E < 0.2 ➔ Clearance is nearly enzyme-dependent e.g. warfarine.
- When E is 0.2 – 0.6 ➔ Clearance depends on both flow and enzymaticdegradation e.g. acetaminophen & chloramphenicol.

Hepatic clearance (Cl_{liver}): is the volume of blood cleared from the drug per unit of time.

CL_{liver} = Extranction ratio (E) X hepatic blood flow (Q)

(4) SYSTEMIC CLEARANCE (CL_S)

- It is the volume of fluid cleared from the drug per unit of time.

CLs = Rate of elimination/Drug concentration

- Systemic clearance is equal to the sum of individual organ clearances i.e. clearance by liver, kidney, lungs…

CLs = Renal clearance (CL_r) + non-renal clearance (CLnr)

Factors affecting drug clearance:

1. Blood flow to the clearing organs (directly proportional).
2. Plasma protein binding of the drug (inversely proportional).
3. Activity of clearing processes e.g. hepatic enzyme, glomerular filtration and secretory processes (directly proportional).

Significance of clearance :

1. Calculation of the maintenance dose (MD) = **CLs X Css.**
2. The dosing regimen of drug eliminated by glomerular filtration can be guided by creatinine clearance e.g. dosing of gentamicin:
   - If kidney function is normal (Cr CL = 120 ml/min.) → dose is 80 mg 3times/day.
   - If kidney function is impaired, you can reduce the dose or increase the dosage interval according to Cr CL:
     - If Cr CL = 60 ml/min, give half the usual dose (40 mg 3times/day).
     - If Cr CL = 30 ml/min, give one quarter the usual dose (20 mg 3times/day) or give the usual dose every 32 hours.

How to icrease duration of action of drugs:

1- ***Delay absorption:***

- Add vasoconstrictor e.g. adrenaline to local anaesthetics.
- Use S.C. pellet implantation.
- Use sustained-release (SR) preparations.
- Add oil to vasopressin.
- Use moderately soluble preparations e.g. protamine zinc insulin suspension.

2- *Decrease metabolism:* use enzyme inhibitors.

3- *Decrease excretion:* probenicid →↓renal secretion of penicillin.

Notes:

- **Loading dose:** The dose required to achieve a desired plasma concentration (desired Css) rapidly, followed by routine maintenance dose.

Loading dose = Vd x desired Css

- **Maintenance dose :** The dose given to maintain the desired Css. i.e. maintenance dose equal eliminated drug in certain period of time.

Maintenance dose = clearance x desired Css

- **Changing the dose** not change the time needed to reach Css but changes Css.
- **Increasing dosing frequency** reduces the amplitude of swings and troughs in drug concentration but the value of Css is constant.